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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,640	07/11/2001	Avi Ashkenazi	10466/85	3104

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EXAMINER	
KATCHEVES, KONSTANTINA T	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,640	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-47 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-47 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 44-47 and 49-51 are pending in the present application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 44-47 and 49-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

Claims 44-47 and 49-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Upon reconsideration of the prior Office actions, the pending claims, the withdrawn rejections and the declaration by Paul Polakis on 11 August 2004, the examiner has reinstated the present rejection.

The claimed invention is drawn to isolated polypeptide of SEQ ID NO:263, which is referred to as PRO343 throughout the specification. The specification discloses the sequencing of a polypeptide, which displayed some homology with proteases. On page 29, line 35 of the specification, Applicant discusses PRO343 in generalities stating that this protein has homology with proteases. Applicant has described neither the proteases that PRO343 is homologous to nor what degree of homology is found. The specification, as filed, does not provide any evidence or guidance suggesting the claimed protein's activity is involved in any particular activity or disease state.

The specification generally asserts that proteases are useful in biological processes including protein digestion, activation, inactivation or modulation of peptide hormone activity *etc.* On page 138, lines 10-14, Applicant states that PRO343 may be used "both *in vivo* for therapeutic purposes and *in* vitro," and that "those of ordinary skill in the art will well know how to employ the . . .PRO343 polypeptides of the present invention for such purposes." Contrary to Applicant's assertion, without a specific asserted or well-established utility not even one of extraordinary skill in the art would be able to use the PRO343 polypeptide. Applicant fails to disclose any use for the specific protein PRO343, nor any fragments and homologues thereof. No evidence or guidance is provided that would suggest to a skilled artisan that there is any utility in using the protein sequence since Applicant has not adequately describe any specific activity for the alleged protein. Applicant's references to PRO343 in the specification are few. Example 41 on page 180, only discloses the isolation of the full-length cDNA clone of PRO343. Table 9 on pages 230-234 only disclose a gene amplification assay wherein PRO343 expression is increased in some tumor cell lines. The mere over expression of a protein without some knowledge as to its function or use would provide neither a specific nor well-established utility. Thereby, it is doubtful whether the protein of PRO343 can be used in any of Applicant's asserted utilities.

Additionally, the specification's lack of a specific and a well established utility is further supported by the specification which notes that a search of the proteins encoded by the claimed sequences merely revealed similarity to proteases in general. See page 29. The accurate prediction of the claimed protein activity cannot be based on primary structure alone. Berendsen (Science Vol.282 1998) teaches that "folding to the stable native state has not yet

occurred and the simulations do not contain any relevant statistics on the process." See page 643, second column. Further supporting Berendsen's teaching of inability to predict activity based on homology, Galperin et al. (Nature Biotechnology Vol.18 2000) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al. also disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science Vol.290 2000) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the above references that one could not possibility predict the function of a protein from structure alone. Moreover, given a mere assertion of homology to proteases and the lack of even basic homology data, Applicant could not possibly have an appreciation for the function of PRO343. Thus, Applicant has failed to establish a specific utility.

Declaration by Dr. Goddard.

Applicant has asserted and provided a declaration by Audrey D. Goddard, Ph.D. in support of the assertion that the gene amplification data provided in the specification are adequate to establish a specific, substantial and credible utility for the claimed PRO343 polypeptide. Applicant points to Example 92 in the specification wherein gene amplification data using TaqMan PCR show that the gene encoding PRO343 showed 1.15-3.82 fold gene amplification in some lung and colon tumors. The declaration of Dr. Goddard in paragraph 6 and paragraph 7 assert that TaqMan PCR has been widely used in the characterization of genes

and is sensitive enough to detect at least a two-fold increase in gene copy number. Paragraph 7 of the declaration further states that it is the opinion of Dr. Goddard that at least a two-fold increase in gene copy number in a tumor sample relative to a normal sample is useful as a diagnositic marker for the presence of a tumor. Although a specific, substantial and credible utility may exist for the polynucleotide encoding PRO343 to detect cancer cells due to increased copy number, the present claims are drawn to the polypeptide PRO343, not the polynucleotide. The increased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity, or role in cancer. As such neither Applicant's arguments nor the declaration by Dr. Goddard provide a specific, credible or substantial utility for the claimed polypeptides.

Declaration by Dr. Polakis

Dr. Polakis asserts that a correlation between copy number and protein expression is found in the lung and colon tumor cells relative to normal cells. Specifically, Dr. Polakis in paragraph 5 of the Declaration states that:

> From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

This observation of a correlation is not persuasive. Declarant has provided a statement regarding the observation of a correlation of the level of protein expressed but does not provide specific data. For example, a baseline showing of protein expression in a normal cell compared directly to protein expression in a lung or tumor cancer cell. Moreover, because Applicant has

not provided specific data, the examiner is unable to ascertain if the "strong correlation," asserted by Declarant, is statistically significant. Additionally, the art discloses that such correlations between mRNA abundance and protein expression in lung adenocarcenoma cells are suspect. Chen et al. found: "no significant correlation between mRNA and protein expression . . . ." See Chen et al. (Molecular & Cellular Poteomics 1.4 page 304.) Chen et al. show that out of 165 protein spots representing 98 genes the only 28 protein spots (21 genes) have statistincally significant coreelation between expression of the protein and mRNA. See Chen et al. page 308-309. This uncertainty in Chen et al. supports the examiners position that the declaration stating that a correlation exists is not sufficient to show that such data is statistically significant.

Therefore, as discussed above, neither the art not the specification as filed provides a specific and substantial asserted utility or a well established utility for the claimed nucleotides or amino acid sequences; thereby, casting doubt on the utility of the claimed invention. The examiner invites Applicant to contact her should Applicant have any questions regarding the present rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER